recombination. Also provided by the invention are methods of using the vectors to treat pathologies, including cancer, in mammals.

Status of the Application

Claims 16-24 and 26-41 are pending in the above-referenced patent application and are currently under examination. Claims 16-24, 26-31, 33, 35, 38 and 40 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 32, 34, 36-37, 39 and 41 also stand rejected under 35 U.S.C. § 112, first paragraph.

The 35 U.S.C. § 112, First Paragraph Rejection

Claims 16-24, 26-31, 33, 35, 38 and 40 stand rejected under 35 USC § 112, first paragraph, because the specification allegedly does not describe the claimed subject matter in such a way so as to enable one of ordinary skill in the art to make and use the invention. Applicants respectfully traverse.

A. The rejection is based on an asserted lack of patentable utility, but does not establish a prima facie case

From a review of the Office Action, it is readily apparent that the basis for this rejection is not that Applicants have failed to teach how to carry out the steps necessary to administer adenoviral vectors to humans or other animals, or how to make such vectors. Indeed, such assertions would have been inappropriate, because Applicants' specification provides more than sufficient guidance regarding suitable vectors, methods and locations of administration, appropriate dosages, and the like. For instance, the specification provides a detailed description of suitable adenoviral vectors on pages 13-16, including suitable promoters, *etc.* for use in expressing a gene of interest. Significantly, the vectors encompassed by Applicants' claims provide an improvement over previously available adenoviral vectors. In particular, the vectors have a partial or total deletion of a protein IX-encoding DNA sequence, which reduces the risk of wild-type (*i.e.*, replication competent) adenoviral vectors in virus preparations for use in diagnostic and therapeutic applications. Tumor suppressor and suicide genes that are suitable for inclusion in the adenoviral vectors used in Applicants' claimed methods are also described in the specification. For instance, tumor suppressors are described at page 16, line 21 to page 20, line 19. Suicide genes are described at, for example, page 27, line 11 to page

28, line 2. The methods necessary to assemble these components into a vector, as taught by Applicants' specification, do not require undue or excessive experimentation; each step in the process involves a method that is routinely carried out by those of skill in the art.

Nor is "undue" experimentation required to administer the adenoviral vectors according to Applicants' claimed methods. Applicants' specification teaches pharmaceutically acceptable carriers that are suitable for use in the claimed methods (*see, e.g.*, page 20, line 35 to page 22, line 27). Moreover, at the time of Applicants' filing date, those of skill in the art had accumulated much knowledge as to how to administer vectors intended for gene therapy of cancer. In fact, Applicants' specification at page 25 cites Larrick and Burck (1991) *Gene Therapy: Application of Molecular Biology*, Elsevier Science Publishing Co., Inc., New York, and Kriegler (1990) *Gene Therapy and Expression: A Laboratory Manual*, W.H. Freeman and Company, New York, as examples of references that teach methods for gene therapy. Applicants' specification provides additional teachings as to how to administer adenoviral vectors to accomplish the claimed methods. For instance, at page 26, lines 10-16, Applicants' specification teaches that the viral vectors can be administered intravenously, by intratumoral injection, by intraperitoneal administration, among other methods. Applicants' specification also teaches suitable dosages and treatment regimes (*e.g.*, at page 26 lines 25-35). Again, each of these administration methods is routinely carried out by clinicians; ***no*** "undue" experimentation is required.

Thus, no step that is required to practice the claimed methods, *e.g.*, making an adenoviral vector and administering the vector to a mammal, requires undue experimentation. Therefore, it is clear that this rejection, although couched in terms of undue experimentation allegedly being required to practice the invention, is actually based on a belief that gene therapy in general lacks utility. However, the Office Action does ***not*** meet the requirements for establishing a lack of utility rejection.

As acknowledged by the MPEP, in the rare cases in which courts have sustained utility rejections under 35 U.S.C. § 101, the rejection was maintained "either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art" (MPEP § 2107, emphasis in original).

The Federal Circuit has explicitly held that "the purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles" *(see, In re Brana,* 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)). The MPEP states that "[t]hese general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. In such cases, the asserted utility is usually clear, the invention is asserted to be useful in treating the particular disorder. If the asserted utility is credible, there is no basis to challenge such a claim on the basis that it lacks utility under 35 USC 101" (*see,* MPEP § 2107 at page 2100-35, emphasis original). The use of gene therapy for the purpose of treating cancer likewise is ***not*** inherently unbelievable and does ***not*** involve implausible scientific principles. Therefore, a 35 USC § 101 rejection of Applicants' claims would be improper.

Given that a 35 USC § 101 rejection is improper, a "lack of utility" rejection under 35 USC § 112, first paragraph is also improper. According to MPEP § 2164.07, "[a] 35 U.S.C. 112, first paragraph, rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under 35 U.S.C. 101. ***In other words, Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. 101 rejection is proper***" (emphasis added). Therefore, because the rejection is based upon an asserted lack of utility, but does not satisfy the requisite standard for making such rejection, Applicants respectfully submit that the rejection is improper and should be withdrawn for this reason alone.

B. The PTO has not established *prima facie* lack of enablement

The PTO has the initial burden of making a *prima facie* case of showing that a claimed invention lacks utility under 35 U.S.C. § 101/112, first paragraph (MPEP § 2107) or is not enabled under 35 U.S.C. § 112, first paragraph (MPEP § 2164.04). The rejection attempts to meet this burden by applying the Wands/Forman factors. However, Applicants respectfully submit that the instant rejection does ***not*** meet the PTO's burden of establishing a *prima facie* case of non-enablement for the following reasons, which are organized under the headings used in the Office Action.

1. Unpredictability of the art

The rejection asserts that the gene therapy art was extremely unpredictable at the time Applicants' invention was made. In support of this rejection, three references are cited. However, Applicants respectfully submit that these references, taken alone, do not provide a true understanding

of the state of the art of gene therapy, and in particular of the use of gene therapy to treat cancer. A much more accurate picture of the state of the art of gene therapy is provided by the number of gene therapy clinical trials that are currently underway, including Phase II and Phase III trials. As of December 1, 1998, 366 gene therapy trials have been published or are underway, of which 230 are directed to cancer gene therapy. Of the 367 gene therapy clinical trials, 32 are in Phase II, and 2 are in Phase III. Fifty-nine of the trials used adenoviral vectors. Importantly, at least 20 of these gene therapy clinical trials had commenced prior to Applicants' priority date. As of September, 2001, 600 gene therapy trials have been published or are underway, of which 376 are directed to cancer gene therapy (Wiley Clinical Trials Database, http://www.wiley.co.uk/wileychi/genmed/clinical/). Of the 600 gene therapy clinical trails, 68 are in Phase II, and 4 are in Phase III. One hundred sixty-four of the trials used adenoviral vectors.

Just obtaining FDA approval to conduct clinical trials in humans requires a demonstration of pharmaceutical efficacy that is more than sufficient to satisfy the requirements for patentability under 35 U.S.C. § 112 and 101. As stated in the MPEP, "[b]efore a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. . . . Thus, as a general rule, if an applicant has initiated clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility" (MPEP § 2107.02, emphasis in original). In the face of the avalanche of clinical trials that have been approved by the FDA, no basis exists for the Office Action's position that the state of the art for gene therapy in general is insufficiently unpredictable for patentability.

2. State of the Art

The rejection then asserts that the gene therapy art at the time of Applicants' invention was poorly developed. Two of the same references cited in support of the previous point are cited in support of this factor. The rejection states that these two references establish that "no gene therapy protocol had been unambiguously proven to be successful *in vivo*" (Office Action, p. 3). However, this is irrelevant, as patentable utility does not require that an invention be "unambiguously proven" *in vivo*. All that is required is that some pharmaceutical activity be established, either by *in vitro* or *in*

vivo tests. MPEP § 2107.02. Applicants' comments regarding point 1 above are equally applicable to this ground of the rejection.

3. Number of Working Examples

According to the rejection, Applicants present no working examples. This statement ignores the experimental data that is provided in the specification. For example, the specification provides experimental data which demonstrate that an adenovirus vector that expresses p53 was effective in greatly reducing the growth of established tumors and significantly enhancing survival times of animals having tumors (*see, e.g.*, Applicants' specification at pp. 41-42, also Figures 10A and 10B). Another example provided *in vitro* and *in vivo* results demonstrating pharmaceutical activity of methods that employed an adenovirus vector that expressed a suicide gene (Experiment III, pp. 45-54, results at pp. 52-54). These results are discussed in more detail below.

According to the MPEP, "an *in vitro* or *in vivo* animal model in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." MPEP § 2164.02. It is the Examiner's burden to "give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model." *Id.* In the instant case, no reasons are set forth.

4. Amount of Guidance Presented by Applicants

The Office Action bases its analysis of this factor on whether or not the *in vitro* and *in vivo* data provided by Applicants relate to treatment of cancer in humans. The legal standard for judging whether data from an *in vitro* assay is sufficient to satisfy the enablement requirement of 35 USC § 112, first paragraph, is whether one of skill in the art would accept the *in vitro* data as reasonably correlating to the asserted *in vivo* activity. A rigorous or an invariable exact correlation is not required. MPEP § 2107.02, *citing Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985). Again, it is the Examiner's burden to "give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model." MPEP § 2164.02. Absolutely no reasons are provided, so the Examiner has not satisfied this burden.

Although not required to further supplement their presumptively correct disclosure, Applicants provide the following additional information and argument. The model system used in the experiments described in Applicants' specification are of a type that is accepted by those of skill in the

art as being reasonably correlated with therapeutic or pharmacological utility of a cancer treatment. Applicants' Experiment II, for example, utilized nude mice into which H69 (small cell lung carcinoma cells) had been introduced, resulting in the establishment of tumors. In *In re Brana*, the Federal Circuit expressly recognized that tumors that arise from introducing tumor cells into nude mice provide an acceptable model system for establishing therapeutic or pharmacological utility of a potential cancer treatment . Moreover, as described in an exhibit submitted previously in a response to an Office Action, the H69 cells used in Applicants' experiments are derived from an actual tumor (a small cell human lung carcinoma from a 55 year old male) and are accepted for use in screening of cancer treatments by the National Cancer Institute. In *Brana*, the Federal Circuit gave significant weight to the use of a cell line that was recognized as suitable by the NCI (*In re Brana*, 34 USPQ2d at 1442).

Furthermore, as described in a press release from Schering-Plough Corporation on November 23, 1998 (submitted previously as an exhibit in a response to an Office Action), Applicants' claimed methods were found to exhibit encouraging results in an ongoing Phase I clinical trial. More recently, Applicants' claimed methods were found to exhibit encouraging results in a study in combination with chemotherapy. Phase III studies of the claimed methods are currently under way (*see,* attached press release of Schering-Plough, November 23, 1998; Exhibit 1). The M.P.E.P. states that "as a general rule, if an applicant has initiated clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility" (MPEP § 2107.02, emphasis in original). Therefore, the subject matter of Applicants' claimed methods must be presumed to satisfy the standard for utility under 35 USC § 112, first paragraph.

5. Scope of the Claims

According to the rejection, the claims read broadly on treatment of any of thousands of different pathologies in animals or humans. However, Applicants note that the pending claims are limited to tumors and tumor cells. Furthermore, some of Applicants' claims are directed to narrower embodiments than the broadest claims. For example, claim 24 is limited to a particular mode of administration (intratumoral), claim 29 is limited to a particular type of tumor cells (hepatocellular carcinoma). No discussion is provided by the Office Action as to the narrower embodiments.

6. Nature of the Invention

This factor is merely a repetition of the first and second factors discussed above and does not add new evidence or reasoning to support the rejection. Therefore, Applicants' responses to the first and second factors are applicable to this ground of the rejection.

7. Level of Skill in the Art

Applicants agree that the level of skill in the gene therapy art is high. Applicants do not agree, however, that those of preeminent skill in the art were unable to reduce to practice successful gene therapy years after the priority date. To the contrary, as discussed above, many gene therapy studies (including those of Applicants) have shown sufficient pharmaceutical utility to satisfy the enablement/utility requirement of 35 USC § 112, first paragraph.

In summary, Office Action does not establish a *prima facie* case of nonenablement.

C. Applicants' Experimental Results are Sufficient to Overcome a *Prima Facie* Case of Non-Enablement

Even if the Office Action had established a *prima facie* case of non-enablement, which it has not, Applicants' specification contains sufficient *in vitro* and *in vivo* experimental data to overcome the *prima facie* case. According to the MPEP, "[i]f reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process." MPEP § 2107.02(a)(emphasis added).

Applicants' specification demonstrates that the claimed methods can reduce tumor growth *in vivo*. Experiment II (pp. 32-45) describes an experiment in which an adenoviral vector of the invention which carried a gene encoding the tumor suppressor p53 was found to greatly reduce the growth of established tumors and significantly enhance survival times of animals having these tumors (*see, e.g.*, Applicants' specification at pp. 41-42, also Figures 10A and 10B). The last of the control adenovirus-treated animals died on day 83, while all five animals treated with a p53-expressing vector were still alive 130 days after tumor cell inoculation.

Applicants' specification also provides experimental results from an experiment in which a different *in vivo* system was used to demonstrate the efficacy of an adenovirus that expressed

a suicide gene (Experiment III, pp. 45-54, results at pp. 52-54). Adenoviral vectors that express HSV-tk were introduced into three different hepatocarcinoma lines *in vitro* and, in conjunction with ganciclovir treatment, shown to inhibit cellular proliferation (Figure 14, Table 2 at p. 53). An *in vivo* experiment in which established tumors in mice were treated with the adenoviral vectors and ganciclovir in accordance with the methods of the invention resulted in a reduction of tumor size at day 58, although the difference in tumor size did not reach statistical significance. Thus, Applicants have established that the claimed methods exhibit pharmacological utility in both *in vitro* and *in vivo* systems.

In summary, *prima facie* non-enablement has not been established by the instant Office Action. Moreover, Applicants' have provided *in vitro* and *in vivo* data which demonstrate that the claimed methods have pharmacological utility. Under well-established case law, these data would be sufficient to overcome a *prima facie* case of non-enablement, had such case been established. Therefore, Applicants respectfully submit that this ground of rejection is improper and should be withdrawn.

D. Applicants' New Claims Satisfy the Enablement Requirement of 35 USC § 112, First Paragraph

Applicants have added to the application new claims 32-41, which are directed to methods for obtaining expression of a tumor suppressor gene in a cell (claims 32-36) and for obtaining expression of a suicide gene in a cell (claims 37-41). As do the previously pending claims, Applicants' new claims satisfy the enablement requirement of 35 USC § 112, first paragraph. The methods of claims 32-41 are fully supported by experimental data that is present in Applicants' specification. For example, experimental data at page 37 demonstrate that p53 protein is expressed by cells into which adenoviral vectors that contained the p53 gene were introduced.

Moreover, although the newly added claims encompass gene therapy, the claimed methods also find use for applications other than cancer therapy. For example, the methods are useful for "safe recombinant production of diagnostic and therapeutic polypeptides and proteins . . . ." (Applicants' specification, p. 14, lines 30-32). Such uses of the claimed methods are sufficient to satisfy the utility requirement of 35 USC §§ 101/112, first paragraph, even aside from the therapeutic uses of the methods. As stated in the MPEP, "[r]egardless of the category of invention that is claimed

(e.g., product or process), an applicant need make only one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112; additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility." MPEP § 2107.01.

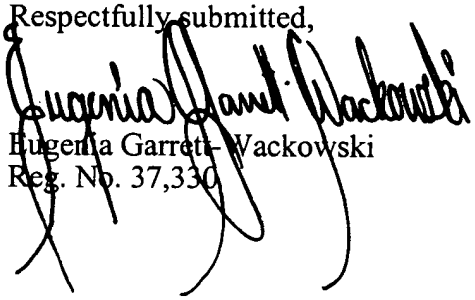
THE 35 U.S.C. § 112, SECOND PARAGRAPH REJECTION

Claim 23 stands rejected under 35 USC § 112, second paragraph as being indefinite. Applicants have amended claim 23 as kindly suggested by the Examiner to replace "and" with --or--. This is believed to obviate this ground of rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 925-472-5000.

Respectfully submitted,



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Publication Year: 2001

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Multi-Dose Intraperitoneal (IP) Rad/ p53 (SCH58500) Gene Replacement Combined with Chemotherapy in Heavily Pretreated Recurrent Ovarian Cancer is Associated with Prolonged Survival.

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Objective: We recently reported the safety of p53 gene replacement with SCH58500 in the treatment of recurrent ovarian cancer. Following completion of dosing with SCH58500 [plusminus] chemotherapy, most subjects went on to additional chemotherapy with a variety of agents. Thus, it is possible to ask whether SCH58500 has a survival impact based upon single- (SD) vs. multi-dose (MD) regimens. Methods: Twelve patients were treated with a single IP dose of SCH58500 at $7.5x10^{10}$ to $7.5x10^{12}$ particles. Forty-one patients were treated with multi-dose IP SCH58500 at $7.5x10^{12}$ to $7.5x10^{13}$ particles for 5 days per cycle. Chemotherapy with a platinum agent [MD-P] [plusminus] paclitaxel was added to the 2nd and 3rd cycles (n=24). Alternatively, a non-platinum regimen [MD-NP] consisting of doxil, gemcitabine, or topotecan was added (n=17). Follow-up treatment of each subject after p53 gene replacement therapy was at the discretion of the referring physician. This study was not randomized, but was a sequential cohort retrospective analysis. Results: Comparisons between SD, MD-P, MD-NP subjects on the basis of age, interval from primary diagnosis to first SCH58500 and number of prior chemotherapy regimens indicated no significant differences. Thirty-three patients, including all SD patients, have died of their disease. Median survival among SD subjects was 5.0 months [range 1.5-24] compared to 13.0 months [range 1.6-35.3^{+}] in the MD-P group and 13.0 months [range 1.0-25.6^{+}] for those treated with a non-platinum based chemotherapy. Fourteen individuals have survived for [greater than or equal to] 20 months. Conclusion: Individuals treated with multi-dose IP SCH58500 combined with chemotherapy survive longer than individuals treated with single dose IP SCH58500 and subsequent chemotherapy. This may be secondary to differences in prior treatments or may represent a therapeutic benefit of SCH58500, which is independent of a platinum continuing regimens. Phase III studies of this agent are underway.